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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Christian Plank, et al.
Application No. : 10/023,317 Confirmation No.: 2272
Filed : December 17, 2001
For : COMBINATIONS FOR INTRODUCING NUCLEIC
ACIDS INTO CELLS
Group Art Unit : 1635
Examiner : Angell, Jon E.

New York, New York
June 22, 2007

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION OF CHRISTIAN PLANK UNDER 37 C.F.R. § 1.132

I, Christian Plank, a citizen of Austria, residing at Ulrich-Haid-Strasse 1, 82229, Seefeld, Germany, hereby declare and state as follows:

1. I am one of the co-inventors of the subject matter described and claimed in the above-identified application.
2. I am currently a research group leader at the Institute of Experimental Oncology and Therapy Research, Technical University, München, Germany. I have held this position since 1997.
3. For the past 17 years, I have studied synthetic constructs for nucleic acid delivery into cells including every step from chemical synthesis, gene vector assembly and biophysics to use of such constructs for nucleic acid delivery in cell cultures and in vivo.

I have attached my curriculum vitae (Exhibit A), which lists my educational background and professional activities. It also lists the articles that I have authored or co-authored and published in peer-reviewed scientific journals and at seminars at various scientific meetings.

4. I have read and am familiar with the February 22, 2007 Office Action in the above-identified application. I understand that, in the Examiner's view, the specification is only enabling for PEI/nucleic acid-P3YE5C, Polylysine/nucleic acid P3INF7, DOTAPcholesterol/nucleic acid-P3YE5C, DOTAP/cholesterol/nucleic acid-P6YE5C, and PEI/nucleic acid-P6YE5C.

5. I make this declaration to demonstrate that a person of ordinary skill in the art, following the teachings of the specification, would be able to obtain the claimed compositions and practice the claimed methods without undue experimentation.

6. Exhibit B depicts the results of experiments carried out by me and/or under my direction. The results demonstrate that two co-polymer formulations—formulations that are not specifically exemplified in the specification of the above-identified application, as filed, but that fall under the definition of Formula I—are able to form complexes with DNA and deliver the DNA into HeLa cells.

7. In the experiments, the cationic peptide SV404 (PKKKRKVG)₄C was synthesized according to the FastMoc™ protocol using an Applied Biosystems® 431A peptide synthesizer. The peptide was purified by reverse phase chromatography, lyophilized and redissolved in deionized water. The peptide was coupled to the intermediates 3 or 4 (see Fig. 1 of the above-identified application) via disulfide bridge formation in complete analogy to what is described in the specification for the peptide (YEEEEEE)₂K-ahx-C (see Fig. 2 of the above-identified application and paragraphs [0146]-[0153] of the published application). The products, designated P6-SV404 and P3-SV404 respectively, were purified by size exclusion chromatography on a Sephadex® 75 size exclusion column with 20 mM HEPES pH 7.4 / 3 M sodium chloride as elution buffer. The product fractions were dialyzed against 20 mM HEPES pH 7.4. The concentrations of the polymers (and at the same time of the coupled peptides) were determined by a ninhydrin assay using the HPLC-purified peptide SV404 as a

calibration standard. Plasmid DNA binding and compaction were determined by dynamic light scattering measurements (Malvern Zetasizer™ 3000HS) as well as by fluorescence quenching measurements using the DNA intercalating dye PicoGreen® (Molecular Probes®). These measurements demonstrated that the copolymers P6-SV404 and P3-SV404 bind and compact DNA.

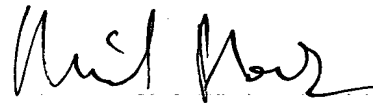
DNA binding and compaction were also determined in the presence of the endosomolytic peptide INF7, which is described in the specification. For this purpose, the peptide INF7 was fluorescence-labeled with fluorescein, the fluorescence of which is quenched when compacted in a DNA complex by a polycation. Plasmid DNA was mixed at various ratios with the fluorescence-labeled peptide and then compacted by the addition of P6-SV404 and P3-SV404, respectively. The measurements demonstrated that P6-SV404 and P3-SV404 readily form DNA complexes comprising the endosomolytic peptide INF7.

In order to demonstrate the potency of P6-SV404 and P3-SV404 in gene delivery, a transfection experiment with the luciferase reporter gene was carried out in HeLa cells. The day prior transfection, 20,000 cells per well were seeded in 96-well plates. Two stock solutions in 20 mM HEPES pH 7.4 were prepared containing plasmid DNA (coding for luciferase under the control of the CMV promoter) and 3 or 1 charge equivalent INF7 (one charge equivalent corresponds to 606 μmol peptide per gram DNA). A dilution series of the copolymers P6-SV404 and P3-SV404, respectively, was prepared in 20 mM HEPES pH 7.4 in a 96-well plate such as to result in charge ratios (positive over negative) of 10, 6.67 and 4.44, 2.96, 1.98, respectively, upon addition of aliquots of the DNA-INF7 stocks. The resulting DNA complexes were serially diluted in 20 mM HEPES pH 7.4 as well in order to derive a dose-response profile in gene delivery. Finally, the dilutions were adjusted to a final glucose concentration of 5 % by addition of a 50 % glucose stock solution. Aliquots of the resulting preparations (50 μl each) were transferred to the cells in triplicates so as to result in DNA doses of 500, 250, 125 and 62.5 ng per well. After 24 h of incubation, the luciferase assay was carried out, as described in the specification. The results demonstrated that both polymers are suitable to mediate gene delivery to cultured cells.

8. The products P6-SV404 and P3-SV404 referred to above and in Exhibit B fall under the general Formula I. In contrast to the polymer products exemplified in the specification (see, e.g., Figures 2 and 3 in the application), P6-SV404 and P3-SV404 are positively charged polymers. These above data demonstrate that charged copolymers of the general Formula I with entirely divergent chemical and physical properties fulfill their intended task in nucleic acid delivery.

9. Based on the teachings of the specification, which are confirmed by the data provided herein, a person of ordinary skill in the art would conclude that copolymers falling under the general Formula I are suitable for nucleic acid delivery into cells.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18, United States Code, and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.



Christian Plank

Signed at Munich, Germany
this 12 day of June, 2007.

Curriculum Vitae

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<i>Date and place of birth:</i>	September 3 rd , 1963, Wels, Austria
<i>Citizenship:</i>	Austrian
<i>Marital Status:</i>	married

PROFESSIONAL EXPERIENCE

- **3/1997-present:** Technische Universität München, Institute of Experimental Oncology
Group leader – artificial virus-like delivery systems for nucleic acids and active agents. Deputy director of the institute. Development of nonviral gene vectors for gene therapy applications. Development of the Magnetofection™ technology (magnetically controlled and targeted nucleic acid delivery). Application of Magnetofection™ in immuno gene therapy of cancer (feline fibrosarcoma) in a veterinary clinical study. Development of magnetic microbubbles as carriers for active agents in drug delivery and in medical imaging. Development of polymers for the shielding and stabilization of nanoparticles ("*Protective Copolymers*"). Development of implantable carrier materials of nucleic acid vectors for tissue engineering, wound, cartilage and bone healing.

- **11/2003:** Foundation of OZ Biosciences S.A.R.L., Marseille, France. This company was founded together with Olivier Zelphati and Jean Haensler, previous colleagues at the University of California in San Francisco. OZ Biosciences develops and markets reagents and technologies for the delivery of active substances to living cells. It caters to the international research community. OZ Biosciences reached it's break-even already in the second year of its existence. See www.ozbiosciences.com.

- **3/1994-11/1997:** University of California-San Francisco, CA, USA.
Postdoctoral Fellow in the laboratory of Prof. Francis C. Szoka Jr., Department of Pharmacy and Biopharmaceutical Sciences. Development of gene delivery systems based on peptides. Biophysical studies for vector characterization. Characterization of the interaction of gene vectors with blood components.

HIGHER EDUCATION AND ACADEMIC DEGREES

2003-2004 Habilitation Technische Universität München, Medical Faculty. 2003 submission of the Habilitation thesis with the title „Synthetic nanoconstructs for gene delivery – from design to application“. Degree of „Privatdozent“ and *venia legendi* in 2004.

1990-1994 University of Vienna, Vienna, Austria.

Ph.D. degree (Dr. rer.nat.) in biochemistry, summa cum laude. Title of Ph.D. thesis: "Development of a Synthetic Virus-Like Gene Transfer System". Experimental work for the thesis carried out at the Research Institute of Molecular Pathology (I.M.P.), Vienna, Austria, in the laboratory of Prof. Ernst Wagner, part of the larger research team of Prof. Max L. Birnstiel.

1989-1990 Research Institute of Molecular Pathology (I.M.P.), Vienna.

Diploma thesis "Synthesis and application of biologically relevant peptides". Experimental work for the thesis carried out in the laboratory of Prof. Ernst Wagner.

1983 - 1990 University of Vienna, Vienna, Austria. **Diploma student in biochemistry.** Diploma (*Magister rerum naturalium*) in 1990, summa cum laude.

Application No.: 10/023,317

Response dated June 22, 2007

In Response to February 22, 2007 Office Action

EXHIBIT A

PRIMARY SCHOOL AND HIGH SCHOOL

1970-1974 Primary school (Volksschule) Braunau am Inn / Laab, Austria.

1974-1982 High School. Gymnasium Braunau am Inn. University entrance diploma (Abitur) 1982, summa cum laude. Grade point average 1,0.

HONOURS AND AWARDS

1994-1996. Austrian Academy of Science. Erwin Schrödinger Fellowship.

1996-1997. Max Kade Foundation, New York and Austrian Academy of Science. Max Kade Fellowship.

1998. Award of the Federal Country of Upper Austria for Science („Talentförderungspreis Wissenschaft des Landes Oberösterreich“).

2001. Best of Biotech Business Plan Competition, Vienna. Award among the 10 best-ranked business plans.

2002. Award of the Surgical Work Group Biomaterials of the German Surgical Society.

SERVICE TO PROFESSIONAL PUBLICATIONS

Scientific reviewer for the journals Gene Therapy, Human Gene Therapy, Journal of Gene Medicine, Molecular Therapy, Journal of Vascular Research, Journal of Magnetism and Magnetic Materials, Biomacromolecules, Bionjugate Chemistry, FEBS Journal, Peptides, SMALL, Journal of Controlled Release, Blood, Nucleic Acids Research, Nature Methods, Proceedings of the National Academy of Sciences of the USA and others.

PUBLICATIONS INCLUDING REVIEWED AND PUBLISHED ABSTRACTS

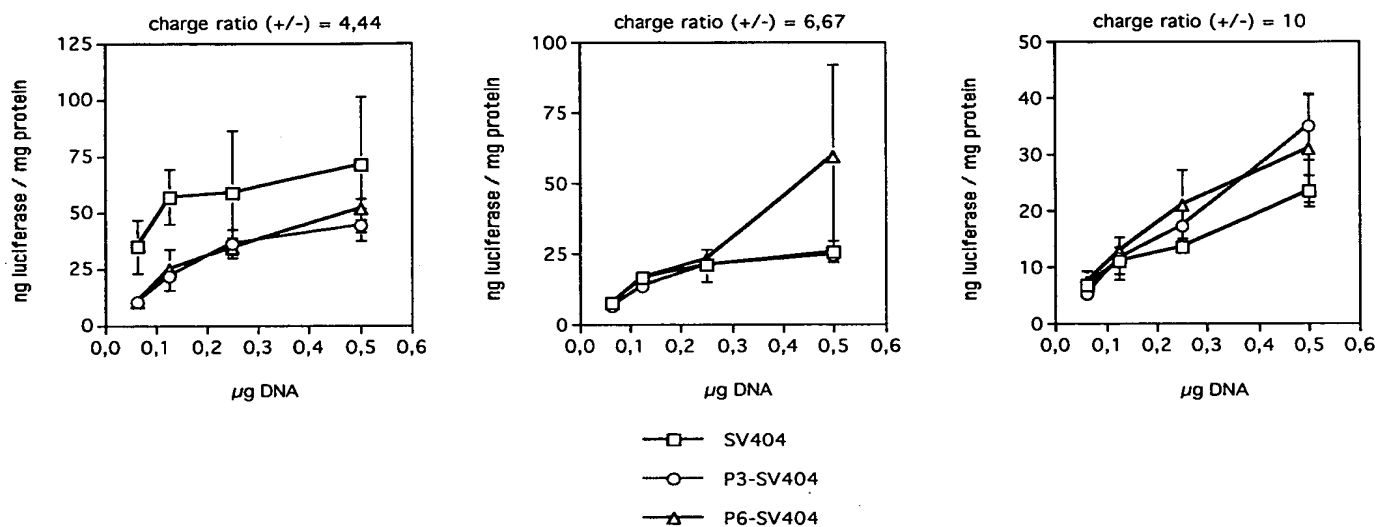
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Exhibit B



Luciferase reporter gene delivery to HeLa cells using the cationic copolymers P3-SV404 and P6-SV404 in comparison with the cationic peptide SV404 (PKKKRKVG)₄C at different charge ratios. DNA complexes were formed together with the endosomolytic peptide INF7. The results demonstrate that the copolymers yield similar transfection efficiencies as the peptide SV404.